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Invasive *Haemophilus influenzae* Disease in Adults ≥ 65 Years, United States, 2011

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Background. Since the introduction of the *Haemophilus influenzae* serotype b vaccine, *H influenzae* epidemiology has shifted. In the United States, the largest burden of disease is now in adults aged ≥ 65 years. However, few data exist on risk factors for disease severity and outcome in this age group.

Methods. A retrospective case-series review of invasive *H influenzae* infections in patients aged ≥ 65 years was conducted for hospitalized cases reported to Active Bacterial Core surveillance in 2011.

Results. There were 299 hospitalized cases included in the analysis. The majority of cases were caused by nontypeable *H influenzae*, and the overall case fatality ratio (CFR) was 19.5%. Three or more underlying conditions were present in 63% of cases; 94% of cases had at least 1. Patients with chronic heart conditions (congestive heart failure, coronary artery disease, and/or atrial fibrillation) (odds ratio [OR], 3.27; 95% confidence interval [CI], 1.65–6.46), patients from private residences (OR, 8.75; 95% CI, 2.13–35.95), and patients who were not resuscitate status (OR, 2.72; 95% CI, 1.31–5.66) were more likely to be admitted to the intensive care unit (ICU). Intensive care unit admission (OR, 3.75; 95% CI, 1.71–8.22) and do not resuscitate status (OR, 12.94; 95% CI, 4.84–34.55) were significantly associated with death.

Conclusions. Within this age group, burden of disease and CFR both increased significantly as age increased. Using ICU admission as a proxy for disease severity, our findings suggest several conditions increased risk of disease severity and patients with severe disease were more likely to die. Further research is needed to determine the most effective approach to prevent *H influenzae* disease and mortality in older adults.

Keywords. *Haemophilus influenzae*; older adults.

Since the introduction of the *Haemophilus influenzae* serotype b (Hib) vaccine, *H influenzae* epidemiology in the United States has shifted; nontypeable *H influenzae* has emerged as the cause of most invasive disease in all age groups [1]. In the United States, adults aged ≥ 65 years now account for the largest proportion of

H influenzae disease, and the risk of disease increases with increasing age [1–3]. The case fatality ratio (CFR) is also highest in this older age group [1, 2].

Few studies have focused on invasive *H influenzae* in persons ≥ 65 years, and as a result there is limited information available on risk factors for disease in this age group [1, 3]. A previous study using Active Bacterial Core surveillance (ABCs) data from 1999 to 2008 described the characteristics of patients with invasive *H influenzae* and assessed risk factors for in-hospital mortality, but it did not focus on older adults [3]. We conducted a case-series review of hospitalized invasive *H influenzae* cases ≥ 65 years identified through an active, population- and laboratory-based surveillance system in the United States to further examine the burden

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of disease, possible risk factors, and the potential impact of underlying conditions on disease severity and outcome.

METHODS

A retrospective case-series review of invasive *H influenzae* infections in patients aged ≥ 65 years was conducted for hospitalized cases reported to ABCs in 2011. Active Bacterial Core surveillance is an active, population- and laboratory-based surveillance system that includes all or part of the following 10 states: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee [4]. Active Bacterial Core surveillance is supported by the Centers for Disease Control and Prevention (CDC) as part of its Emerging Infections Program Network [5]. The population under surveillance was 42 421 940 in 2011 (representing 13.6% of the US population), and the population aged ≥ 65 years under surveillance was 5 326 646.

A case was defined as isolation of *H influenzae* from a normally sterile site (eg, blood or cerebrospinal fluid [CSF]) in a resident of a surveillance area. The standard ABCs case report form collects demographics, clinical syndrome, underlying conditions, serotype, and outcome data abstracted from medical records. Outcome of illness was based on patient status at the time of hospital discharge; no information was collected on whether the death was attributed to *H influenzae* infection.

The clinical syndrome was defined as meningitis if a clinical diagnosis of meningitis was reported in the medical record or if *H influenzae* was isolated from the CSF. The syndrome was defined as pneumonia if pneumonia was reported in the medical record and *H influenzae* was isolated from blood or pleural fluid. If no clinical syndrome was listed in the medical record and *H influenzae* was isolated from blood, then the syndrome was defined as bacteremia.

Available isolates for all *H influenzae* cases were sent to the CDC for confirmation by *Haemophilus* quad identification plates, API Neisseria-*Haemophilus* strips, and polymerase chain reaction (PCR) [6–8]. *Haemophilus influenzae* serotype was determined by slide agglutination or serotype-specific real-time PCR assays.

An expanded case report form was used to collect additional information from the medical record on hospitalized cases: residence location at time of initial culture; other underlying conditions not collected by the ABCs case report form including cognitive dysfunction, recent upper or lower respiratory tract infections, active or inactive tuberculosis, and atrial fibrillation; symptoms and physical examination findings at admission; information on any recent surgeries, tests, procedures, and interventions conducted during hospital stay (chest x-ray or chest computed tomography [CT], mechanical ventilation, respiratory support, do not resuscitate [DNR] status, antibiotic use, subsequent positive cultures, and culture confirmation of other

invasive illnesses); intensive care unit (ICU) admission and duration of stay; diagnoses and ICD-9/10 codes at discharge; and discharge location.

Estimates of the prevalence of coronary artery disease (CAD), congestive heart failure (CHF), and current smoking among adults ≥ 65 years were obtained from the 2009–2010 National Health and Nutrition Examination Survey (NHANES) for comparison to the prevalence among cases of *H influenzae* [9]. NHANES uses a nationally representative sample and oversamples the population ≥ 60 years to ensure reliable statistics. The sample does not include persons living in nursing homes or other institutions. The prevalence of chronic obstructive pulmonary disease (COPD), atrial fibrillation, diabetes, dementia, and hypertension in adults ≥ 65 years was obtained from the literature [10–14].

Estimated average annual incidence rates of invasive *H influenzae* infections in adults ≥ 65 years were calculated for the United States using 2009 through 2011 census data and are reported per 100 000 population. For incidence calculations only, ABCs case reports from 2009 through 2011 were used. A multiyear range was used to obtain more accurate incidence estimates due to small case counts in the individual years. For national incidence estimates, race- and age-specific rates of disease were applied from the aggregate ABCs areas to the race- and age-specific distribution of the US population.

Statistical Analyses

SAS version 9.3 was used for all analyses (SAS Institute, Inc, Cary, NC). Associations were evaluated using the χ^2 test, and the Student's *t* test was used to compare means of continuous variables by outcome and severity of disease. Age was divided into 5 categories (65–69 years, 70–74 years, 75–79 years, 80–84 years, and ≥ 85 years), and trends across these age groups were assessed using the Cochran-Armitage test for trend. Multivariable analysis was performed using logistic regression to determine associations with death or ICU admission.

The study protocol was exempted from review by the CDC, Maryland Department of Health and Mental Hygiene, and Johns Hopkins Institutional Review Boards and was approved by the Georgia Department of Public Health, Emory University, and the Department of Veterans Affairs Institutional Review Boards. No other sites required institutional review board review.

RESULTS

During 2009 through 2011, the estimated average annual incidence of invasive *H influenzae* infections in the United States was 6.50 per 100 000 population in persons aged ≥ 65 years. Incidence was highest for nontypeable *H influenzae* (5.05 per 100 000 population) and increased with age (Table 1).

Three hundred fifteen cases of invasive *H influenzae* infections in patients aged ≥ 65 years were reported from participating ABCs sites in 2011. Of these, 299 (95%) were hospitalized

Table 1. Annual Estimated Incidence (per 100 000) of *Haemophilus influenzae* in Persons Aged ≥65 Years, by Age Group and Serotype, United States, 2009–2011

Age, Years	Serotype			Total [†]
	b	Non-b	Nontypeable	
65–69	0.12	1.19	2.29	3.60
70–74	0.04	1.26	3.74	5.04
75–79	0.05	1.53	4.43	6.01
80–84	0.14	1.33	6.32	7.78
≥85	0	1.80	13.05	14.85
Overall	0.08	1.37	5.05	6.50

[†] Cochran-Armitage test for trend: $P < .0001$.

and had a chart available for review; the following results will focus on these 299 cases. Cases had a median age of 79 years (range, 65–103 years) and a median body mass index in the overweight category (median, 26.0; range, 15.8–57.0). Males accounted for 44% of cases. Most cases were white (83%), non-Hispanic (64%), and living in a private residence (74%) or long-term care facility (19%) at the time of illness onset. Bacteremic pneumonia was the most common clinical syndrome (81%), followed by bacteremia (13%) and meningitis (4%). Thirty cases did not have serotype information available. Among cases with available serotype information, the majority of cases in all age groups were caused by nontypeable *H influenzae* (78%), and the proportion of cases caused by nontypeable *H influenzae* increased with increasing age (Table 2). Serotypes f (12%), e (6%), and a (2%) were all more frequent than serotype b (1%). The highest proportion of both serotype e and f disease was seen in persons aged 65–69 years (Table 2). Fifty-eight (19%) case-patients died. The overall CFR was 19.5% and increased with age, ranging from 10.2% to 27.5% (Table 2); CFR did not differ significantly by serotype or syndrome.

At least 1 underlying condition was present in 94% of cases, with 1 underlying condition in 12% of cases, 2 in 19% of cases, and 3 or more in 63% of cases. The most frequently reported underlying conditions were COPD, CAD, CHF, atrial fibrillation, diabetes, hypertension, dementia, and smoking (Table 3). Chronic obstructive pulmonary disease, CAD, CHF, atrial fibrillation, diabetes, and dementia were all more common in cases than in the general population ≥65 years, whereas hypertension and smoking were less common in cases than the general population [9–14] (Table 3). P values were not calculated for COPD, atrial fibrillation, diabetes, hypertension, or dementia because only percentages were available in the literature. Thirteen percent of cases had been hospitalized in the 60 days before illness onset, and 4% of cases had surgery in the 30 days before illness onset.

Ninety-seven percent of cases had a chest x-ray or chest CT performed within 24 hours of admission. A consolidation or infiltrate was found in 76% of these cases and was reported as a new finding in 84%. Ninety-five percent of cases received antibiotics for at least 3 days, and 60% received more than 1 antibiotic. Seven percent of cases had a subsequent culture positive for *H influenzae*, and 6% of cases had another invasive bacterial infection during hospitalization. One hundred thirty-one cases (44%) were admitted to the ICU; of these, 25% spent more than 1 week in the ICU. Two hundred four cases (68%) required some form of respiratory support, and 59 cases (20%) required mechanical ventilation during hospitalization. Of those requiring mechanical ventilation, 97% were admitted to the ICU. Forty-nine (85%) of the cases that died were DNR status upon admission.

Based on multivariable analysis using backward selection, patients with chronic heart conditions (CHF, CAD, or atrial fibrillation), patients from private residences, and patients who were DNR status were more likely to be admitted to the ICU (OR, 3.27; 95% CI, 1.65–6.46; OR, 8.75; 95% CI, 2.13–35.95; and OR, 2.72; 95% CI, 1.31–5.66, respectively). In univariable analyses looking at mortality, cases that died were older

Table 2. Serotype and Case Fatality Ratio by Age Group for Hospitalized Cases of *Haemophilus influenzae* aged ≥65 years, Active Bacterial Core Surveillance, 2011

Age, Years	Serotype* no. (%)					Case Fatality Ratio [‡]
	a	b	e	f	Nontypeable [†]	
65–69	0	2 (3.5)	8 (14.0)	14 (24.6)	33 (57.9)	10.2
70–74	3 (7.0)	0	1 (2.3)	7 (16.3)	32 (74.4)	14.3
75–79	2 (5.3)	0	2 (5.3)	4 (10.5)	30 (79.0)	17.4
80–84	0	1 (2.6)	2 (5.1)	2 (5.1)	34 (87.2)	20.9
≥85	1 (1.1)	0	3 (3.3)	6 (6.5)	82 (89.1)	27.5
Overall	6 (2.2)	3 (1.1)	16 (6.0)	33 (12.3)	211 (78.4)	19.4

* Thirty cases were excluded due to missing serotype information.

[†] Cochran-Armitage test for trend: $P < .0001$.

[‡] Cochran-Armitage test for trend: $P = .0039$.

Table 3. Prevalence of Common Underlying Conditions in Hospitalized *Haemophilus influenzae* Cases Reported to ABCs in 2011 and the General Population Aged ≥65

Underlying Condition	<i>H influenzae</i> Cases ≥65 Years	General Population ≥65 Years*	P Value†
COPD	36.0%	7.2%–11.2%	
CAD	34.6%	11.4%	<.0001
CHF	32.8%	7.2%	<.0001
Atrial Fibrillation	29.2%	3.8%–9.0%	
Diabetes	28.4%	20.1%–20.7%	
Hypertension	17.1%	67%	
Dementia	15.0%	6%–10%	
Smoking	12.1%	18.4%	.0074

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

* [9–14].

† Test for significant difference between the 2 proportions, P values calculated where possible.

($P = .0050$), more likely to live in a long-term care facility than a private residence ($P = .0002$), more likely to present with shortness of breath ($P = .0263$), more likely to have been admitted to the ICU ($P = .0001$), and more likely to be DNR status ($P < .0001$). In a multivariable analysis using backward selection, only ICU admission (OR, 3.75; 95% CI, 1.71–8.22) and DNR status (OR, 12.94; 95% CI, 4.84–34.55) were significantly associated with death. All results were similar when nontypeable *H influenzae* were analyzed alone.

CONCLUSIONS

This is the first review of factors related to *H influenzae* disease and outcome focused on adults ≥65 years using multistate, population-based surveillance data. This study confirms previous reports in the post-Hib vaccine era of the relatively high burden of invasive *H influenzae* disease in adults ≥65 years, especially pneumonia caused by nontypeable *H influenzae* [1–2, 15–19]. Within this older age group, incidence and the CFR both increased significantly as age increased. Although nontypeable *H influenzae* causes most invasive disease in adults ≥65 years, we also found that disease caused by serotypes f and e was more prevalent than serotype b disease, which is consistent with previous studies on non-b disease in older adults [2, 19, 20].

The most common underlying conditions found in this review were consistent with previous findings from ABCs sites [3]. However, they differed from underlying conditions identified in other studies of *H influenzae* infections among all adults (cancer, immunosuppressive conditions, and alcohol abuse) conducted outside of ABCs [15–19]. Chronic obstructive pulmonary disease, CAD, CHF, atrial fibrillation, and diabetes

were the most common underlying conditions in our study, each reported by over 25% of cases, and they were more common than in the general population aged ≥65 years. Chronic obstructive pulmonary disease and diabetes have been reported as underlying conditions in other studies of person aged ≥18 years but in lower proportions than we observed [15, 18, 19]. Coronary artery disease, CHF, and atrial fibrillation are not commonly reported underlying conditions associated with *H influenzae* disease in persons aged ≥18 years [15, 16, 18, 19]. However, in 1 small study of *H influenzae* cases in the elderly, similar proportions of COPD and atrial fibrillation and higher proportions of CAD were seen [17]. It is unclear whether these underlying conditions increased risk for invasive disease or are just coexisting conditions.

Using ICU admission as an indicator of disease severity, patients with severe disease were more likely to die, but none of the underlying conditions evaluated in this study were found to be associated with death. Other underlying conditions not listed on the chart review form or not available in the chart could potentially be associated with death, but further assessment would be needed. Our data also suggest that patients with chronic heart conditions or DNR status and those living in private residences had more severe *H influenzae* disease. However, it is also possible that patients with chronic heart conditions were admitted to the ICU because of their underlying heart condition and not as a result of more severe *H influenzae* disease. Patients from private residences may wait longer to seek medical care than those patients from long-term care facilities and as a result present with more severe disease on admission.

The majority of cases in our study were living in a private residence at the time of illness onset, and thus likely acquired the disease in the community. It is difficult to identify the source of community-acquired infection; in susceptible older adults, pharyngeal colonization or invasive upper respiratory infections may progress to invasive disease. Although asymptomatic nasopharyngeal colonization with *H influenzae* does occur, the relationship between carriage and disease development is not well understood. Few data exist on carriage of typeable *H influenzae* in adults, but several studies suggest overall *H influenzae* carriage may be as high as 42% [21–23]. Because typeable *H influenzae* is one of the leading causes of invasive upper respiratory infections, including otitis media, conjunctivitis, and sinusitis [24, 25], older adults living with or caring for young children may have increased exposure to typeable *H influenzae*.

This study highlights the burden of invasive *H influenzae* in older adults, with incidence increasing with age. A better understanding of the source of invasive *H influenzae*, such as from invasive upper respiratory infection or nasopharyngeal colonization, would aid in determining appropriate prevention strategies. Among older adults, prevention strategies such as vaccination have many challenges, including an overall low disease burden, reduced immunogenicity, and barriers to attaining high coverage.

Increased early recognition of *H influenzae* in older adults may reduce the severity of illness in cases, but the diagnosis can be challenging in persons with multiple comorbidities. Further research is needed to determine the most effective approach to prevent *H influenzae* disease and mortality in older adults.

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